

University of Groningen

Cerebral Metabolic Patterns In Neurodegeneration

Meles, Sanne

DOI:
[10.33612/diss.118683600](https://doi.org/10.33612/diss.118683600)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Meles, S. (2020). *Cerebral Metabolic Patterns In Neurodegeneration*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen. <https://doi.org/10.33612/diss.118683600>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

9. The Alzheimer's Disease Metabolic Brain Pattern in Mild Cognitive Impairment

Sanne K. Meles¹, Marco Pagani^{2,3}, Dario Arnaldi⁴, Fabrizio De Carli⁵, Barbara Dessi⁴, Silvia Morbelli⁶, Gianmario Sambuceti⁶, Cathrine Jonsson⁷, Klaus L. Leenders^{1*}, Flavio Nobili^{4*}

¹Department of Neurology, University of Groningen, University Medical Center Groningen, The Netherlands

²Institutes of Cognitive Sciences and Technologies, CNR, Rome, Italy

³Department of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden

⁴Clinical Neurology, Department of Neuroscience (DINO GMI), University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy

⁵Institute of Molecular Bioimaging and Physiology - C.N.R. - Genoa Unit. Italy
AOU San Martino-IST, Genoa, Italy

⁶Nuclear Medicine, Department of Health Sciences (DISSAL), University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy

⁷Medical Radiation Physics and Nuclear Medicine, Imaging and Physiology, Karolinska University Hospital, Stockholm, Sweden

*Shared last author

J Cereb Blood Flow Metab. 2017 Dec 37(12):3643-3648

Abstract

We investigated the expression of the Alzheimer's disease-related metabolic brain pattern (ADRP) in ¹⁸F-FDG PET scans of 44 controls, 27 patients with mild cognitive impairment (MCI) who did not convert to Alzheimer's disease (AD) after five or more years of clinical follow-up, 95 MCI patients who did develop AD dementia on clinical follow-up, and 55 patients with mild-to-moderate AD. The ADRP showed good sensitivity (84%) and specificity (86%) for MCI-converters when compared with controls, but limited specificity when compared with MCI non-converters (66%). Assessment of ¹⁸F-FDG PET scans on a case-by-case basis using the ADRP may be useful for quantifying disease progression.

Introduction

Mild cognitive impairment (MCI) marks the transition between normal cognitive function and Alzheimer's disease (AD) dementia. However, some MCI patients remain stable throughout their entire observed clinical course, and may even revert to normal cognition (Pandya et al., 2016). Discriminating between non-converters and patients with pre-dementia AD is important for patient management and for future clinical trials. However, this is not easily achieved by clinical evaluation alone.

^{18}F -Fluoro-deoxyglucose positron emission tomography (^{18}F -FDG PET) may aid in this differentiation (Dubois et al., 2014). ^{18}F -FDG PET provides an index of brain glucose metabolism, which reflects synaptic activity and integrity (Reivich et al., 1979). AD pathology induces synaptic dysfunction in specific, connected brain regions. These downstream brain changes result in decreased ^{18}F -FDG uptake in posterior temporo-parietal regions.

Patterns of altered ^{18}F -FDG uptake can be extracted with the Scaled Subprofile Model and Principal Component Analysis (SSM PCA), a well-studied multivariate method (Spetsieris, Eidelberg, 2011). Disease-related patterns identified by SSM PCA not only delineate the disease topography, but can also be used to quantify new ^{18}F -FDG PET scans. For quantification, normalized scans are projected onto a previously-identified disease pattern to calculate a subject score. The subject score reflects the degree to which the pattern is present in a subject's scan. This method was previously shown to be successful in the differential diagnosis of parkinsonian disorders (Tang et al., 2010b, Tripathi et al., 2015), in predicting disease onset in prodromal individuals with Parkinson's disease (Holtbernd et al., 2014), and in evaluating disease progression and treatment effects (Huang et al., 2007, Meles et al., 2017a, Tang et al., 2010a).

In a previous study, we identified an AD-related pattern (ADRP) in 15 AD patients and 18 controls studied at the University Medical Center Groningen using SSM PCA. The ADRP was characterized by relative hypometabolism of the posterior temporo-parietal cortical areas (Figure 1), and was expressed in new patients with AD, but not in healthy elderly. In addition, ADRP subject scores correlated significantly with neuropsychological test performance (Teune et al., 2014). The ADRP has also been identified by two other groups (Habeck et al., 2008, Mattis et al., 2016). It has been shown that the ADRP is superior at identifying AD patients compared to univariate, region-of-interest approaches (Habeck et al., 2008). Further validation of our ADRP (Teune et al., 2014) in a larger cohort is necessary. Moreover, it is unknown whether ADRP subject scores can discriminate between non-AD and AD at the MCI stage.

In this study, we further validate the ADRP (Teune et al., 2014) by computing its expression in a large cohort of healthy controls, MCI patients with

long-term clinical follow-up, and AD patients. Our main objective was to determine whether ADRP subject scores could discriminate between MCI-converters and MCI non-converters at baseline.

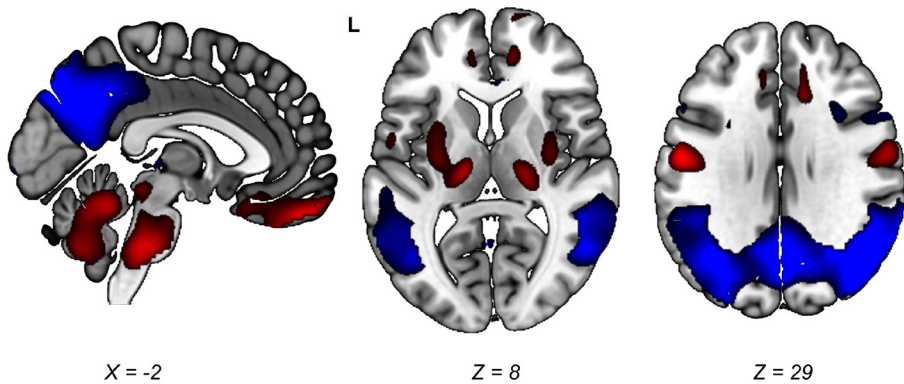


Figure 1. Topography of the Alzheimer's Disease-related pattern (ADRP). The ADRP was identified in ^{18}F -FDG PET data of 18 healthy controls and 15 AD patients, anatomically registered to an ^{18}F -FDG PET template (for details see (Teune et al., 2014)). Stable voxels in the ADRP were determined with a bootstrap resampling method (1000 repetitions, one-sided confidence interval threshold of 90%) and overlayed onto a T1 MRI template to show the most salient regions in the pattern. L=Left. Relatively hypermetabolic areas are color-coded red, and relatively hypometabolic areas are color-coded blue.

Methods

Participants

^{18}F -FDG PET data from healthy aged subjects (normal ageing, NA; $n=42$), patients with MCI ($n=122$) and patients with AD dementia at the time of the PET scan ($n=55$) were analyzed from a previous study (Supplementary Table 1) (Pagani et al., 2016, Pagani et al., 2017). Patients with MCI ($n=122$) were separated into three groups: patients who did not progress during follow-up (non-converter MCI; ncMCI, $n=27$), patients who progressed to AD after ≥ 2 years of follow up (early MCI; eMCI; $n=34$), and MCI patients who progressed to AD within 2 years of follow-up (late MCI, lMCI; $n=61$). The study was approved by the institutional review board of the University of Genoa, and all subjects gave written informed consent to undergo ^{18}F -FDG PET in the framework of a long-term observational study, in accordance with the Declaration of Helsinki.

^{18}F -FDG PET Data Analysis

^{18}F -FDG PET data were acquired and pre-processed as described previously (Pagani et al., 2016). We calculated ADRP subject scores in all ^{18}F -FDG PET scans as follows: First, ^{18}F -FDG PET images were masked to remove out-of-brain voxels. Next, each image was log-transformed and both the subject mean and reference group mean were removed. The group mean was previously determined in the ADRP identification cohort (Teune et al., 2014). These operations resulted in a subject residual profile (SRP) for each scan. Finally, a subject score (SS) for each subject was computed based on the ADRP by taking the inner product of the two vectors, the ADRP and SRP ($\text{SS} = \text{SRP} * \text{ADRP}$) (Spetsieris, Eidelberg, 2011).

The ^{18}F -FDG PET data investigated in this study was acquired on a different PET system than the cohort which was originally used for ADRP identification (Teune et al., 2014). To account for the effect of camera differences on ADRP expression, ADRP subject scores were z -transformed to the NA group, such that the NA mean was 0 with a standard deviation of 1.

In the ADRP identification cohort (Teune et al., 2014), we determined the threshold ADRP z -score with optimum sensitivity and specificity using a receiver-operating curve. This threshold was determined to be $z=0.8$ and subsequently applied to the new ADRP z -scores in this study. ADRP z -scores ≥ 0.8 were considered to be indicative of AD. A visual representation of the ADRP (Teune et al., 2014) that was used in this study is provided in Figure 1.

Statistical Analysis

ADRP subject z -scores were compared across NA, ncMCI, eMCI, IMCI, and AD subjects with a one-way analysis of variance (ANOVA) with post hoc Bonferroni corrections. With the threshold of $z=0.8$, we identified the number and percentage of subjects correctly classified in each group. Sensitivity, specificity, accuracy, and area under the receiver-operating characteristic curve (AUC-ROC) were determined for the comparisons: NA versus AD patients, NA versus MCI-converters + AD patients, NA versus MCI-converters alone, ncMCI versus MCI-converters + AD patients, and finally, ncMCI versus MCI-converters.

Pearson's r correlation coefficient was used to test the correlation between the parametric variables of ADRP z -scores and age. Correlations between ADRP z -scores and non-parametric variables (MMSE corrected for educational level and age, time to conversion, and education) were tested for significance with a Spearman rank correlation coefficient. All analyses were performed using SPSS software version 23 (SPSS Inc., Chicago, IL), and results were considered significant when $P<0.05$ (two-tailed).

Results

ADRP z -scores were significantly different between groups ($F=36.33$, $P<0.0001$). ADRP z -scores were significantly higher in MCI-converters and AD patients compared with both NA and ncMCI patients (Figure 2). Table 1 shows the sensitivity, specificity, accuracy, and AUC-ROC for the different group comparisons. Specificity in the ncMCI category was limited (66.66%).

Supplementary Table 1 shows the percentage of correctly-classified subjects per category based on ADRP z -scores. Nine out of 27 ncMCI had a supra-threshold ADRP z -score. Follow-up time in these nine individuals ranged from a minimum of 6.8 to a maximum of 9.8 years.

ADRP z -scores were not significantly correlated to time-to-conversion in MCI-converters ($\rho=-0.05$, $P=0.66$). A significant relationship was observed between ADRP z -scores and MMSE (MCI-converters + AD patients; $\rho=-0.341$; $P<0.0001$; Supplementary Figure 1).

In the ncMCI group, ADRP z -scores appeared to be higher in patients with a higher education (Supplementary Figure 2A), with borderline statistical significance ($\rho=0.375$, $P=0.054$). Furthermore, a significant relationship between age and ADRP z -scores was only present in the ncMCI group ($r=0.502$, $P=0.008$; Supplementary Figure 2B). ADRP z -scores did not correlate significantly to age or education in the other groups.

Table 1. Diagnostic Performance of the ADRP

	NA versus AD dementia	NA versus MCI-converters + AD dementia	NA versus MCI-converters	ncMCI versus MCI-converters + AD dementia	ncMCI versus MCI-converters
Sensitivity	90.90	86.66	84.21	84.61	84.21
Specificity	85.57	85.57	85.71	66.66	66.66
Accuracy	0.87	86.46	0.84	81.97	80.33
AUC-ROC	0.95	0.91	0.89	0.84	0.80

AD = Alzheimer's Disease, ADRP = AD-related pattern; AUC-ROC = Area under the curve of the receiver operating characteristic; MCI = mild cognitive impairment; ncMCI = non-converter MCI; NA = normal ageing

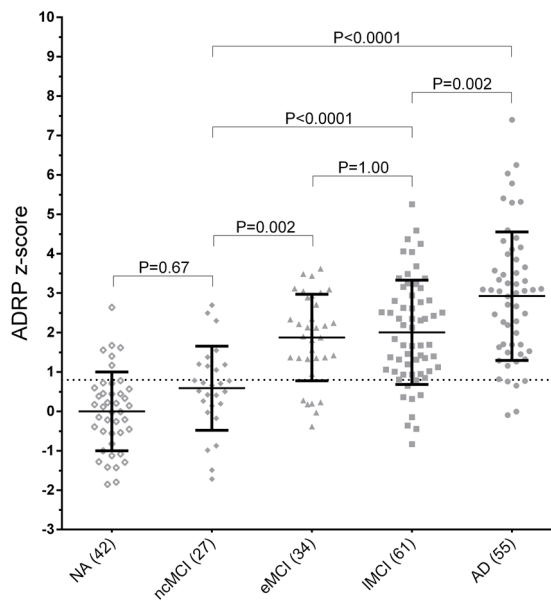


Figure 2. ADRP z-scores across groups. All ADRP subject scores were z-transformed to NA. Group differences were tested for significance with a one-way ANOVA; post hoc comparisons were Bonferroni-corrected.

AD = Alzheimer's disease; ADRP = Alzheimer's disease-related pattern; MCI = mild cognitive impairment; NA = normal ageing; ncMCI = non-converting MCI; eMCI = early MCI; lMCI = late MCI.

Discussion

We studied expression of the AD-related pattern (ADRP) in baseline ^{18}F -FDG PET scans of a large cohort of MCI patients with clinical follow-up. ADRP subject z -scores were significantly higher in MCI patients who progressed to AD dementia compared with both healthy elderly and non-converting MCI patients. In line with a previous study, ADRP z -scores were significantly correlated to disease severity in AD (measured by the MMSE score) (Teune et al., 2014). Compared with healthy elderly, we found good sensitivity (84.2%) and specificity (85.7%) of the ADRP for the detection of early brain dysfunction in AD (i.e., NA versus MCI-converters).

Specificity of the ADRP was limited in the non-converting MCI group (66.7%), as one-third of ncMCI patients (9/27) had a supra-threshold ADRP z -score. Even though clinical follow-up in these patients was long (5.0-9.8 years), such cases cannot simply be interpreted as false-positives. Some may still develop AD dementia on further follow-up. To illustrate, one late-converting MCI patient had a baseline ADRP z -score of 3.11 and only developed clinical AD 8 years later.

It could also be hypothesized that non-converting MCI patients with a supra-threshold ADRP score have a larger cognitive reserve. Such individuals are able to maintain a certain level of cognitive functioning, despite having temporo-parietal hypometabolism (Garibotto et al., 2008). Individuals with a higher education have a larger cognitive reserve, and are thought to have the ability to recruit compensatory networks involving the dorsolateral prefrontal cortex (Morbelli et al., 2013). In line with this, we found higher ADRP z -scores in MCI non-converters with a higher education. The non-linear relationship between hypo-metabolism and the clinical manifestation of the disease may also explain why ADRP z -scores did not correlate significantly to time-to-conversion in the pre-dementia AD group.

An alternative explanation for the limited specificity in the ncMCI group may be that the ADRP reflects the underlying abnormalities in neuronal networks in AD, but is not pathology-specific (Dubois et al., 2014). MCI is a common manifestation in many conditions (Ritchie, 2004). The finding that ADRP z -scores were only correlated to age in the ncMCI group may indicate that ncMCI patients with a supra-threshold ADRP z -score have a non-AD pathology which progresses with age, and affects cortical areas which partially overlap with the ADRP topography. Although patients who met the criteria for vascular cognitive impairment were excluded (Pagani et al., 2016), mild cerebrovascular disease in combination with other factors (drug therapy, chronic disease, and depression) may have resulted in ADRP-like metabolic changes in the ncMCI group.

While our main objective was to examine whether ADRP scores could adequately differentiate between MCI-converters and non-converters, a second objective of this study was to validate the ADRP which was previously identified in a

cohort of AD patients and controls in Groningen (Teune et al., 2014). We successfully applied the ADRP to a completely independent dataset. We note that other multivariate approaches were also applied to the data presented in this study (Pagani et al., 2016, Pagani et al., 2017), and gave similar sensitivity and specificity for AD. An important advantage of the current approach is that the ADRP could be applied to new subjects on a single case-by-case basis, despite these subjects having been scanned on a different PET system.

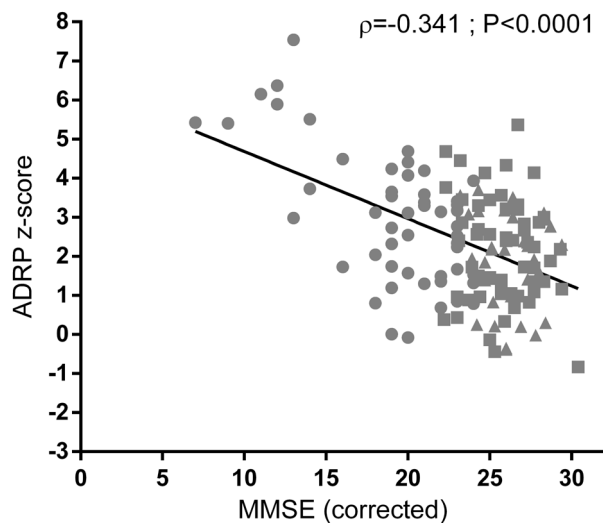
Along with anatomic brain imaging, amyloid PET, and cerebrospinal fluid analysis, expert visual reading of ^{18}F -FDG PET scans is an accepted ancillary investigation in the diagnostic work-up of cognitive decline (Morbelli et al., 2015, Dubois et al., 2014). A single-case analysis in which separate brain regions are identified where ^{18}F -FDG uptake levels deviate from normal can also be achieved with univariate, semi-quantitative SPM-based methods (Perani et al., 2016). A limitation of semi-quantitative methods is that it is difficult to objectively quantify progression of metabolic changes. The ADRP may be especially useful to measure disease progression, and may thus provide important complementary information to a semi-quantitative visual reading of ^{18}F -FDG PET in clinical practice.

Supplemental Material for Chapter 9

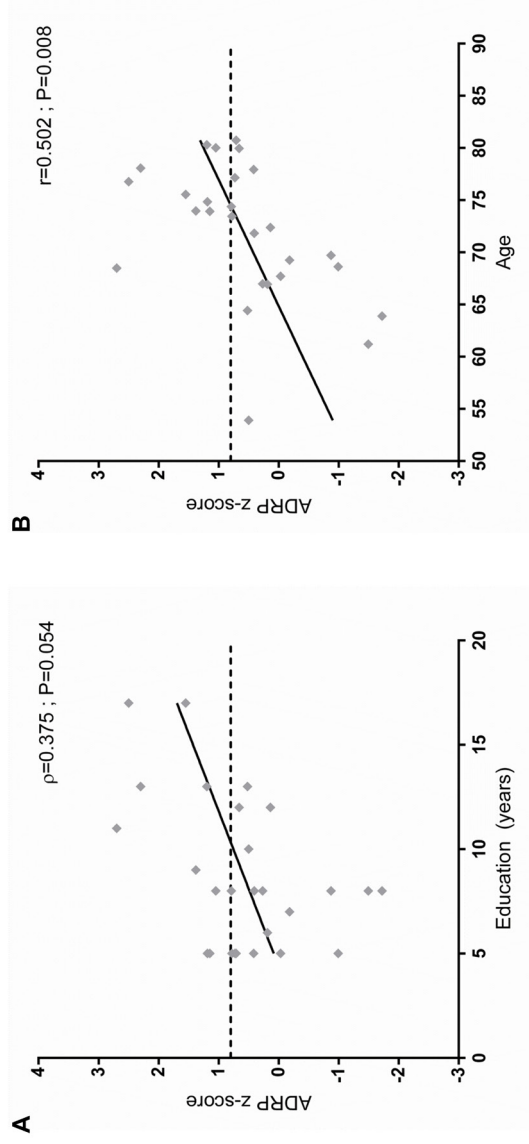
Supplementary Table 1

Group	NA	ndMCI	eMCI	IMCI	AD
n	42	27	34	61	55
Age	68.29±9.64	72.00±6.61	75.19±6.70	75.18±6.70	73.43±7.36
Gender: n male (%)	11 (26)	15 (55)	8 (23)	23 (38)	19 (34)
MMSE at baseline*	29.0 (29.0-30.0)	27.0 (26.0-28.0)	26.3 (24.7-28.0)	25.9 (24.3-27.1)	20.0 (18.0-23.0)
Years of follow-up		7.53±1.51 (5.02-9.79)	4.86±1.86 (2.04-10.30)	3.24±1.39 (0.51-7.05)	
Years to AD conversion			3.08±1.33 (2.02-8.25)	1.15±1.33 (0.08-1.99)	
MMSE at conversion*			22.0 (21.0-24.0)	23 (21-24)	
n subjects with ADRP	6	9	28	52	50
z≥0.80 (positive test)					
n subjects with ADRP	36	18	6	9	5
z<0.80 (negative test)					
% correctly classified	85.71	66.67	82.35	85.21	90.91
ADRP score	0±1	0.59±1.07	1.87±1.10	2.00±1.32	2.92±1.63

Values are given as mean ± standard deviation with the range in parentheses unless specified with (), which indicates median with interquartile range in parentheses.
AD = Alzheimer's disease; ADRP = Alzheimer's disease-related pattern; MCI = mild cognitive impairment; NA = normal ageing; ndMCI = non-converting MCI; eMCI = early MCI; IMCI = late MCI



Supplementary Figure 1. *ADRP subject z-scores in MCI converters and AD patients combined correlate significantly to MMSE scores. Early MCI (eMCI) are indicated by triangles, late MCI (lMCI) are indicated by squares, and Alzheimer's disease patients (AD) are indicated by circles. ADRP = AD related pattern; MMSE = mini-mental state examination.*



Supplementary Figure 2: Correlations in the non-converting MCI (ncMCI) Group. (A) There is a trend of increasing ADRP z-scores in ncMCI patients with a higher education. (B) ADRP z-scores were significantly correlated to age in the ncMCI group.

